3,5-Disubstituted 6-Benzyl-1,2,4-triazines: Syntheses and Reactions

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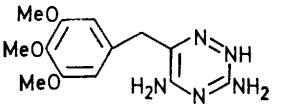
3,5-Diamino-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazine (1) has been obtained by the action of ammonia on 3,5-bismethylthio-, 3,5-dithioxo-, or 3-methylthio-5-thioxo-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazine, and by treatment of 3-amino-5-oxo-6-(3,4,5-trimethyoxybenzyl)-1,2,4-triazine with phenyl phosphorodiamidate. Displacement reactions of thioxo- and methylthio-groups in the 3- and 5-positions of the 1,2,4-triazine nucleus show that the 5- is considerably more reactive than the 3-position.

SEVERAL 1,2,4-triazines show pronounced antimalarial,[1a-c] antimicrobial,[2] and antiviral activity.[3] We have briefly reported the synthesis of 3,5-diamino-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazine (1), the 6-aza-analogue [4] of the antimalarial Trimethoprim, and now describe other products obtained in this synthesis, as well as the preparation of related 1,2,4-triazines and their reactions.

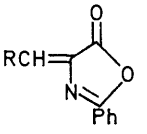
The most direct route to 6-substituted 3,5-diamino-1,2,4-triazines involves the condensation of a pyruvonitrile with aminoguanidine hydrogen carbonate salt in nitric acid and dimethyl sulphoxide at 25 °C, followed by cyclization of the product in ethanolic potassium hydroxide. This scheme has been used [1b,c,5] to prepare various 6-substituted 3,5-diamino-1,2,4-triazines, but has never been successful in the synthesis of 6-benzyl derivatives. An attempt [1b] to prepare the triazine (1) by the cited procedure showed that the condensation between aminoguanidine hydrogen carbonate and 3,4,5-trimethoxyphenylpyruvonitrile did not take place. Another attempted route to 3,5-diamino-1,2,4-triazines involving treatment of 3,5-dichloro-1,2,4-triazines with ammonia was similarly unsuccessful.[6a,b] These results prompted us to explore alternative routes.

3,4,5-Trimethoxybenzaldehyde and *N*-benzoylglycine were condensed to give 2-phenyl-4-(3,4,5-trimethoxybenzylidene)-Δ^2-oxazolin-5-one (2). The azlactone (2) was converted into (3,4,5-trimethoxyphenyl)pyruvic acid *via* sodium hydroxide-induced hydrolysis followed by treatment with sulphur dioxide and acidification with hydrochloric acid. Condensation of the oxo-acid with thiosemicarbazide in ethanol in the presence of acetic acid gave the corresponding thiosemicarbazone. Cyclization was effected by heating this compound with potassium carbonate and then acidifying the reaction mixture to afford 3,4-dihydro-3-thioxo-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazin-5(2*H*)-one (3). Treatment of (3) with phosphorus pentasulphide in boiling pyridine gave the corresponding 3,5-dithione (3a). Methylation of (3) with sodium ethoxide and methyl iodide in ethanol afforded the 3-methylthio-derivative (4). Thiation of (4) gave 3-(methylthio)-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazine-5(2*H*)-thione (4a). Methylation of (3a) and (4a) resulted in 3,5-bis(methylthio)-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazine (5).

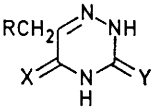
The reactions of compounds (3a), (4a), and (5) with methanolic ammonia in an autoclave were examined. Compound (3a) gave a mixture of the diamine (1), the 3-amino-5-oxo derivative (4b), and the 3,5-dioxo-derivative (3b), in 10, 40, and 16% yield, respectively. The reaction of (5) with ammonia afforded compounds



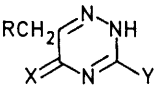
(1)



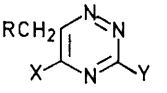
(2) R=3,4,5-$(MeO)_3C_6H_2$·CH_2



(3) X=O, Y=S
(3a) X=Y=S
(3b) X=Y=O
(3c) X=S, Y=O



(4) X=O, Y=SMe
(4a) X=S, Y=SMe
(4b) X=O, Y=NH_2
(4c) X=O, Y=morpholino
(4d) X=O, Y=NHPh
(4e) X=O, Y=NH·N:CMe_2



(5) X=Y=SMe
(5a) X=NH_2, Y=SMe
(5b) X=Y=NH·CH_2Ph
(5c) X=$NHNAc_2$, Y=SMe

(1), (4), (4b), (3b), and (5a) in 10, 20, 17%, trace, and 38% yields, respectively. The reaction of compound (3a) with ammonia in hexamethylphosphoric triamide gave only compound (4b), in 40% yield.

[1] (*a*) G. H. Hitchings, P. B. Russell, and N. Whittaker, *J. Chem. Soc.*, 1956, 1019; (*b*) R. W. A. Rees, P. B. Russell, T. J. Foell, and R. E. Bright, *J. Medicin. Chem.*, 1972, **15**, 859; (*c*) L. C. March, G. S. Bajwa, J. Lee, K. Wasti, and M. M. Joullié, *ibid.*, 1976, **19**, 845.

[2] A. K. Mansour, S. B. Awad, and S. Antoun, *Z. Naturforsch.*, 1974, **29***B*, 792.

[3] S. Watanabe and T. Ueda, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 1551.

[4] K. Wasti and M. M. Joullié, *Heterocycles*, 1976, **4**, 1341.

[5] J. A. Settepani and A. B. Borkovec, *J. Heterocyclic Chem.*, 1966, **3**, 188.

[6] (*a*) C. Grundmann, H. Schroeder, and R. Ratz, *J. Org. Chem.*, 1958, **23**, 1522; (*b*) A. Piskala, J. Gut, and F. Sorm, *Coll. Czech. Chem. Comm.*, 1975, **40**, 2680.

The identity of 5-amino-3-(methylthio)-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazine (5a) was confirmed by its isolation when (4a) was treated with ammonia. The yields of compounds (1), (4b), (3b), and (5a) obtained in this reaction were 23, 27, 2, and 15%, respectively.

Proof of structure for compound (4b) was provided by its formation *via* the reaction of the triazine (3) or (4) with ammonia.

When refluxed briefly with dilute hydrochloric acid, compounds (4), (4a), and (5) were hydrolysed to 6-(3,4,5-trimethoxybenzyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (3b).

The reaction of (4b) with phenyl phosphorodiamidate at 230 °C for 1 h in the presence of ammonium chloride as catalyst also afforded the diamine (1).

The thioxo-groups in (3a) and methylthio-groups in (5) were displaced with benzylamine. In both instances, 3,5-bis(benzylamino)-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazine (5b) was obtained as a monohydrate which could not be dehydrated even by heating *in vacuo* at 80 °C for 3 days. An attempt to prepare the diamine (1) *via* catalytic debenzylation of (5b) (ethanolic solution treated for 8 h in a Parr hydrogenator with a catalytic amount of either Pd–C or Raney nickel) was unsuccessful.

When compound (5) was heated with hydrazine in acetic acid and acetic anhydride, only the 5-methylthio-group was replaced, to give 5-(2,2-diacetylhydrazino)-3-(methylthio)-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazine (5c), identified by synthesis from (4a) and hydrazine under the same conditions.

A few displacement reactions of the methylthio-group in compound (4) were also investigated. Treatment of (4) with morpholine or aniline gave the 3-morpholino- or 3-anilino-derivative, (4c or d). When (4) was refluxed with hydrazine in methanol containing a trace of acetone, the 3-hydrazino-derivative could not be isolated. Only its condensation product with acetone (4e) was formed.

Thiation of compound (3b) with phosphorus pentasulphide in pyridine for 3 h gave the 5-thioxo-derivative (3c). Prolonged heating of the reaction mixture (6 h) produced (3c) and the 3,5-dithioxo-derivative (3a). Alkylation of (3c) with methyl iodide in ethanolic sodium ethoxide gave 2-methyl-5-(methylthio)-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazin-3-(2*H*)-one (6).

EXPERIMENTAL

M.p.s were determined with a Thomas–Hoover Unimelt apparatus and are corrected. Microanalyses were carried out by Robertson Laboratory, Florham Park, New Jersey. I.r. spectra were obtained with a Perkin-Elmer 521 double-beam grating spectrophotometer equipped with a caesium bromide optics; the spectra were run for potassium bromide discs. ^{1}H N.m.r. spectra were obtained with a Varian A-60A, HA-100D, or JEOL-JNM-PS-100 instruments (tetramethylsilane as internal standard). Mass spectra were obtained with a Finnigan F-3 300 instrument with data system 6 000 (ionizing potential of 30 eV). U.v. spectra were obtained with a Beckman DB double-beam spectrophotometer (1.0 cm quartz cells). T.l.c. separations were carried out on plastic-backed plates of silica gel with fluorescent indicator (Baker-flex IB-F). Column chromatography was performed with silica gel (Woelm) of activity grade III (30 mm). The reactions at elevated pressures were carried out in a Parr 4562 pressure reaction apparatus equipped with automatic temperature controller. Samples said to be identical were compared by i.r. and n.m.r. spectroscopy and mixed m.p.

2-*Phenyl*-4-(3,4,5-*trimethoxybenzylidene*)-Δ^2-*oxazolin*-5-*one* (2).—A mixture of 3,4,5-trimethoxybenzaldehyde (98.1 g, 0.5 mol), *N*-benzoylglycine (95.0 g, 0.53 mol), acetic anhydride (150 ml), and sodium acetate (40 g) was refluxed on a steam-bath for 2.5 h, cooled to room temperature, and then slowly treated with absolute ethanol (450 ml). The mixture was kept at 0 °C overnight. The yellow needle-like *crystals* that formed were filtered off, washed with absolute ethanol (100 ml), and dried; yield 120 g (71%), m.p. 166—168° (Found: C, 66.25; H, 5.1; N, 4.2. $C_{19}H_{17}NO_5$ requires C, 66.05; H, 5.25; N, 4.3%).

(3,4,5-*Trimethoxyphenyl*)*pyruvic Acid*.—The azlactone (2) (120 g, 0.35 mol) and sodium hydroxide (550 ml) aqueous 15% were heated under reflux for 2.5 h. The mixture was cooled in an ice-bath and sulphur dioxide was bubbled through. After 10 min, a white precipitate formed. The gas flow was continued for another 10 min, to complete the reaction. The solid was filtered off and discarded. The filtrate was heated to boiling and acidified with concentrated hydrochloric acid (300 ml). The resulting solution was cooled to room temperature and the white crystals that formed were filtered off, washed with water, and dried; yield 60 g (67%), m.p. 177—179° (lit.,[7] 167—168°) (Found: C, 56.4; H, 5.55. Calc. for $C_{12}H_{14}O_6$: C, 56.7; H, 5.55%).

(3,4,5-*Trimethoxyphenyl*)*pyruvic Acid* 2-(*Thiosemicarbazone*).—(3,4,5-Trimethoxyphenyl)pyruvic acid (12.7 g, 50 mmol) was dissolved in hot ethanol (125 ml) and added to a hot solution containing acetic acid (10 ml) and thiosemicarbazide (4.6 g, 50 mmol) in water (150 ml). The mixture was heated under reflux for 1.5 h and then set aside overnight at room temperature. The white fluffy *crystals* that formed were filtered off, washed with water, and dried; yield 15 g (92%), m.p. 203—205° (Found: C, 47.65; H, 5.3; N, 12.75; S, 10.1. $C_{13}H_{17}N_3O_5S$ requires C, 47.7; H, 5.25; N, 12.85; S, 9.8%).

3,4-*Dihydro*-3-*thioxo*-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazin*-5(2H)-*one* (3).—A mixture of (3,4,5-trimethoxyphenyl)-pyruvic acid 2-(thiosemicarbazone) (15 g, 45 mmol), potassium carbonate sesquihydrate (12 g), and water (100 ml) was heated under reflux for 2 h. The solution was cooled to room temperature and then treated dropwise with glacial acetic acid until no further effervescence occurred. The yellow *solid* that formed was filtered off; yield 10 g (72%), m.p. 219—220° (from ethanol) (Found: C, 50.3; H, 4.9; N, 13.65; S, 10.4. $C_{13}H_{15}N_3O_4S$ requires C, 50.45; H, 4.9; N, 13.6; S, 10.35%); $\nu_{max.}$ (KBr) 3 460vw, 3 150m, 3 080w, 2 930m, 1 685vs, 1 590s, 1 525m, 1 420s, 1 225vs, 1 120vs, and 1 000s cm^{-1}; δ [$(CD_3)_2SO$] 3.62 (3 H, s, *para*-ArOMe), 3.72 (8 H, s, *meta*-ArOMe and $ArCH_2$), 6.53 (2 H, s, ArH), 13.05br (1 H, s, H-2), and 13.27br (1 H, s, H-4); *m/e* 309 (M^+); $\lambda_{max.}$ (MeOH) 272 (log ε 4.62).

6-(3,4,5-*Trimethoxybenzyl*)-1,2,4-*triazine*-3,5(2H,4H)-*dithione* (3a).—Solutions of compound (3) (3.0 g, 0.01 mol) and phosphorus pentasulphide (2.3 g, 0.01 mol) in boiling anhydrous pyridine (20 and 40 ml, respectively) were combined. The mixture was heated at reflux for 2 h, then left to cool overnight, and the supernatant pyridine solution

[7] J. Michalský and L. Sadilek, *Monatsh.*, 1959, **90**, 171.

was decanted and evaporated to dryness. The residue, a red oil, was dissolved in 20% sodium hydroxide (50 ml). The alkaline solution was filtered with suction through a bed of moist activated charcoal and acidified (Congo Red). The precipitate was collected and recrystallized from absolute ethanol to give a yellow *product* (3a) (1.3 g, 40%), m.p. 231—233° (Found: C, 48.25; H, 4.8; N, 12.85; S, 19.4. $C_{13}H_{15}N_3O_3S_2$ requires C, 48.0; H, 4.65; N, 12.9; S, 19.7%); $\nu_{max.}$ (KBr) 3 260m, 3 200m, 1 700m, 1 595s, 1 570m, 1 530vs, 1 510vs, 1 460s, 1 420s, 1 380m, 1 320vs, 1 250vs, and 1 165vs cm^{-1}; δ [$(CD_3)_2SO$] 3.66 (3 H, s, *para*-ArOMe), 3.76 (6 H, s, *meta*-ArOMe), 4.05 (2 H, s, $ArCH_2$), 6.61 (2 H, s, ArH), and 13.83br (2 H, s, H-2 and -4); *m/e* 325 (M^+); $\lambda_{max.}$ (MeOH) 274 nm (log ε 4.78).

3-(*Methylthio*)-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazin*-5-(2H)-*one* (4).—To a solution of ethanolic sodium ethoxide [from sodium (0.6 g, 0.025 g atom) and ethanol (400 ml)] were added compound (3) (6.5 g, 21 mmol) and methyl iodide (2 ml). The solution was refluxed for 0.5 h and then set aside at room temperature overnight. The precipitate was collected and recrystallized from glacial acetic acid to give *plates* (5.0 g, 74%), m.p. 244—247° (Found: C, 52.15; H, 5.05; N, 12.95; S, 10.05. $C_{14}H_{17}N_3O_4S$ requires C, 52.15; H, 5.0; N, 13.05; S, 9.95%); $\nu_{max.}$ (KBr) 3 500vw, 3 140vw, 1 620vs, 1 580vs, 1 500s, 1 450s, 1 420s, 1 295s, 1 250s, and 1 230vs cm^{-1}; δ [$(CD_3)_2SO$] 2.48 (3 H, s, SMe), 3.63 (3 H, s, *para*-ArOMe), 3.74 (6 H, s, *meta*-ArOMe), 3.80 (2 H, s, $ArCH_2$), 6.57 (2 H, s, ArH), and 13.70br (1 H, s, H-2); *m/e* 323 (M^+); $\lambda_{max.}$ (MeOH) 270 nm (log ε 5.20).

3-(*Methylthio*)-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazine*-5-(2H)-*thione* (4a).—Solutions of compound (4) (3 g, 9 mmol) and phosphorus pentasulphide (1.8 g, 9 mmol) in boiling pyridine (20 and 40 ml, respectively) were mixed and refluxed for 6 h. The product was then isolated as in the preparation of compound (3a). Recrystallization from 75% ethanol afforded yellow fluffy *needles* (1.5 g, 49%), m.p. 186—189° (Found: C, 49.65; H, 5.0; N, 12.25; S, 18.8. $C_{14}H_{17}N_3O_3S_2$ requires C, 49.55; H, 5.05; N, 12.4; S, 18.9%); $\nu_{max.}$ (KBr) 2 760m, 1 585s, 1 500s, 1 450m, 1 420s, 1 330m, 1 290m, 1 250s, 1 220s, and 1 115vs cm^{-1}; δ ($CF_3 \cdot CO_2D$) 2.73 (3 H, s, SMe), 3.73 (6 H, s, *meta*-ArOMe), 3.78 (3 H, s, *para*-ArOMe), and 4.1 (2 H, s, $ArCH_2$); *m/e* 339 (M^+); $\lambda_{max.}$ (MeOH) 268 nm (log ε 4.75).

3,5-*Bis*(*methylthio*)-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazine* (5).—(A) *From* 6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazine*-3,5-(2H,4H)-*dithione* (3a). To a solution of ethanolic sodium ethoxide [from sodium (92 mg, 4 mmol) and ethanol (50 ml)] were added compound (3a) (650 mg, 2 mmol) and methyl iodide (0.3 ml). As the reaction mixture was shaken, white fluffy *crystals* formed (466 mg, 67%), m.p. 145—146° (from ethanol) (Found: C, 50.95; H, 5.65; N, 11.7; S, 17.95. $C_{15}H_{19}N_3O_3S_2$ requires C, 50.95; H, 5.4; N, 11.9; S, 18.15%) $\nu_{max.}$ (KBr) 2 920m, 1 590vs, 1 500vs, 1 460m, 1 420s, 1 350s, 1 320s, 1 290vs, 1 240s, 1 210s, and 1 120vs cm^{-1}; δ ($CF_3 \cdot CO_2D$) 2.73 (6 H, s, SMe), 3.73 (6 H, s, *meta*-ArOMe), 3.78 (3 H, s, *para*-ArOMe), and 4.05 (2 H, s, $ArCH_2$); *m/e* 353 (M^+); $\lambda_{max.}$ (MeOH) 332 and 220 nm (log ε 3.77 and 4.27).

(B) *From* 3-(*methylthio*)-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazine*-5(2H)-*thione* (4a). Compound (4a) (170 mg, 0.5 mmol) was treated with ethanolic sodium ethoxide (10 ml) [from sodium (0.012 g)] and methyl iodide (0.05 ml) as in the preceding experiment. The white compound (100 mg, 57%) obtained was identical with the material prepared from compound (3a).

Reaction of 3,4-*Dihydro*-3-*thioxo*-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazin*-5(2H)-*one* (3) *with Ammonia*.—A mixture of compound (3) (3.5 g, 11 mmol) and absolute methanol (100 ml) presaturated with dry ammonia gas was heated in a sealed bomb at 175 °C (600 lb in^{-2}) for 6 h. After cooling overnight, the mixture was filtered and the solution was concentrated *in vacuo*. The solid that formed was filtered off and the filtrate was retained. The solid was crystallized from ethanol–water to give off-white *crystals* (4b) (0.6 g, 19%), m.p. 274—276° (decomp.) (Found: C, 53.3; H, 5.65; N, 19.05. $C_{13}H_{16}N_4O_4$ requires C, 53.4; H, 5.5; N, 19.2%); $\nu_{max.}$ (KBr) 1 655s, 1 635s, 1 590m, 1 520m, and 1 130vs cm^{-1}; δ [$(CD_3)_2SO$] 3.61 (3 H, s, *para*-ArOMe), 3.78 (8 H, s, $ArCH_2$ and *meta*-ArOMe), 6.54 (2 H, s, ArH), 6.74 (2 H, s, NH_2), and 11.91 (1 H, s, H-4); *m/e* 292 (M^+); $\lambda_{max.}$ (MeOH) 266 nm (log ε 4.58). The filtrate was concentrated to give a viscous oil which was triturated twice with boiling ethanol and left at room temperature for 2 days. Light yellow crystals (0.45 g) were obtained. Concentration of the mother liquor gave a light yellow gum which was transformed slowly into a semisolid. The semisolid was heated with water (5 ml). When the resulting solution cooled, an additional crop (0.2 g) of the product crystallized. The product fractions were combined and recrystallized from boiling water (120 ml) [with activated carbon (0.1 g)] to give the *dione* (3b) (0.5 g, 16%), white crystals, m.p. 187—189° (Found: C, 53.2; H, 5.3; N, 14.15. $C_{13}H_{15}N_3O_5$ requires C, 53.25; H, 5.15; N, 14.35%); $\nu_{max.}$ (KBr) 3 260m, 1 720vs, 1 695vs, 1 595m, and 1 130s cm^{-1}; δ [$(CD_3)_2SO$] 3.71 (3 H, s, *para*-ArOMe), 3.80 (8 H, s, $ArCH_2$ and *meta*-ArOMe), 6.65 (2 H, s, ArH), 11.95 (1 H, s, H-2), and 12.11 (1 H, s, H-4); *m/e* 293 (M^+); $\lambda_{max.}$ (MeOH) 268 nm (log ε 4.56).

Reaction of 3-(*Methylthio*)-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazin*-5(2H)-*one* (4) *with Ammonia*.—Treatment of compound (4) (2 g, 6 mmol) with methanolic ammonia as in the previous experiment yielded compounds (4b) and (3b) in 47 and 19% yields respectively.

Reaction of 6-(3,4,5-*Trimethoxybenzyl*)-1,2,4-*triazine*-3,5-(2H,4H)-*dithione* (3a) *with Ammonia*.—(A) *In methanol*. A mixture of compound (3a) (2.5 g, 7.68 mmol) and absolute methanol (75 ml) presaturated with ammonia was heated at 150—160 °C and 400—500 lb in^{-2} for 2 h. The mixture was cooled, filtered, and concentrated *in vacuo* to 30 ml. The solid that formed was filtered off and crystallized from methanol–water to give compound (4b) (0.9 g, 40%), m.p. 274—276° (decomp.). The filtrate remaining after the separation of (4b) was concentrated *in vacuo* to 1 ml and was then chromatographed on a silica gel column (ethyl acetate). Evaporation of the fraction with R_F *ca.* 0.77 afforded compound (3b) (0.35 g, 16%). Elution of the column with methanol afforded an off-white solid, m.p. 194—197°. Crystallization gave 3,5-*diamino*-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazine* (1) (0.21 g, 10%), m.p. 197—200° (from water) (Found: C, 53.3; H, 6.1; N, 23.85. $C_{13}H_{17}N_5O_3$ requires C, 53.6; H, 5.9; N, 24.05%); $\nu_{max.}$ (KBr) 3 520m, 3 485m, 3 345m, 1 620s, 1 585s, 1 550m, 1 530m, and 1 120vs cm^{-1}; δ [$(CD_3)_2SO$] 3.61 (3 H, s, *para*-ArOMe), 3.71 (6 H, s, *meta*-ArOMe), 3.87 (2 H, s, $ArCH_2$), 6.03 (2 H, s, NH_2), 6.60 (2 H, s, ArH), and 6.75 (2 H, s, NH_2); *m/e* 291 (M^+); $\lambda_{max.}$ (MeOH) 300 and 224sh nm (log ε 3.74 and 4.34).

(B) *In hexamethylphosphoric triamide*. Compound (3a) (1.0 g, 3 mmol) was dissolved in dry hexamethylphosphoric triamide saturated with dry ammonia. The mixture was heated at 150—170 °C for 2 h as in (A). The solvent was distilled off under reduced pressure and the resulting black

gum was chromatographed on a silica gel column (methanol). Elution of the column with methanol and evaporation of the eluate afforded a black tar from the first two fractions and an off-white solid from the last three fractions. The solid (0.35 g, 40%), m.p. 272—274°, was identical with compound (4b).

Reaction of 3,5-*Bis*(*methylthio*)-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazine* (5) *with Ammonia*.—Compound (5) (1.9 g, 5.3 mmol) was treated with methanolic ammonia as in the preceding experiment. The cooled mixture was filtered and concentrated *in vacuo* to give a dark yellow oil which was then dissolved in absolute ethanol (50 ml) and treated with activated carbon. After filtration, the ethanolic solution was allowed to evaporate at room temperature. The light brown gum that formed solidified upon trituration with boiling benzene. The solid was treated with ethanol, filtered off, and crystallized from methanol–water to give (4b) (0.26 g, 17%), m.p. 272—274° (decomp.).

The filtrate was concentrated and then chromatographed on a silica gel column (ethyl acetate). The fraction with R_F *ca.* 0.7 afforded a light yellow oil on evaporation. The oil was triturated with boiling benzene to yield a semisolid (m.p. 120—130°) which, in turn, was crystallized twice from benzene to afford the *methylthio-amine* (5a) (0.65 g, 38%), m.p. 148—150° (Found: C, 52.15; H, 5.7; N, 17.1; S, 9.85. $C_{14}H_{18}N_4O_3S$ requires C, 52.15; H, 5.6; N, 17.35; S, 9.95%); $\nu_{max.}$ (KBr) 3 490m, 3 410m, 3 290m, 1 630vs, 1 590s, 1 550m, 1 350s, and 1 280s cm^{-1}; δ [$(CD_3)_2SO$] 2.46 (3 H, s, SMe), 3.62 (3 H, s, *para*-ArOMe), 3.72 (6 H, s, *meta*-ArOMe), 3.97 (2 H, s, $ArCH_2$), 6.63 (2 H, s, ArH), and 7.52 (2 H, s, NH_2); *m/e* 322 (M^+); $\lambda_{max.}$ (MeOH) 266 and 230 nm (log ε 4.68 and 4.44).

† For details of Supplementary Publications see Notice to Authors, No. 7, *J.C.S. Perkin I*, 1975, Index issue.

The fraction with R_F *ca.* 0.6 gave a semisolid product which was crystallized twice from absolute methanol to yield compound (4) (0.35 g, 20%), m.p. 244—247°.

Concentration of the mother liquor afforded traces of a white solid, m.p. 187—189°, identical with compound (3b).

Elution of the column with methanol gave a light brown solid, m.p. 195—198°, which was crystallized from water to yield compound (1) (0.16 g, 10%), as off-white crystals, m.p. 197—200°.

Reaction of 3-(*Methylthio*)-6-(3,4,5-*trimethoxybenzyl*-1,2,4-*triazine*-5(2H)-*thione* (4a) *with Ammonia*.—Treatment of compound (4a) (1.5 g, 4.4 mmol) with methanolic ammonia as in the previous experiment gave compounds (4b) (0.34 g, 27%), (3b) (0.03 g, 2%), (5a) (0.21 g, 15%), and (1) (0.3 g, 23%).

Hydrolysis of 3-(*Methylthio*)-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazin*-5(2H)-*one* (4), 3-(*Methylthio*)-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazine*-5(2H)-*thione* (4a), *and* 3,5-*Bis*(*methylthio*)-6-(3,4,5-*trimethoxybenzyl*)-1,2,4-*triazine* (5).—Compounds (4), (4a), and (5) were heated under reflux with an excess of dilute hydrochloric acid (25% v/v) for 15 min. The solution was cooled and the solid thus obtained crystallized from water to give compound (4b) (67—80%), m.p. 189—190°.

The preparations of compounds (3c), (4c—e), (5b and c), and (6) and the reaction of compound (4b) with phenyl phosphorodiamidate are described in Supplementary Publication No. SUP 21878 (6 pp.).†

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